Chapter 14: Varicella

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I. Disease Description

Varicella (chickenpox) is the primary infection caused by the varicella-zoster virus (VZV). Humans are the only source of infection for this virus. Varicella is highly infectious with secondary infection rates in susceptible household contacts approaching 90%. Transmission occurs from person-to-person by direct contact with patients with either varicella or zoster lesions, or by airborne spread from respiratory secretions. The incubation period for varicella is 10-21 days, most commonly 14-16 days. Varicella is characterized by a pruritic, maculo-papulo vesicular rash that evolves into noninfectious, dried crusts over a 5- to 6-day period. The disease is usually mild among children. A prodrome of fever and constitutional symptoms precedes the rash by 1-3 days. A person with varicella is contagious from 1 to 2 days before the rash appears until all of the vesicles have formed scabs.

Varicella severity and complications are increased among immunocompromised persons, neonates, children less than 1 year of age, and adults.[1] However, healthy children and adults may also develop serious complications and even die from varicella.[2-5] Serious complications include secondary bacterial infections (most notably those caused by group A beta-hemolytic streptococcus including cellulitis, necrotizing fasciitis, septicemia and toxic shock syndrome), pneumonia, encephalitis, cerebellar ataxia, Reye syndrome, and death.

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Infants born to women who developed varicella within the period of 5 days before delivery to 2 days after delivery are at risk of neonatal varicella, which may be severe. Congenital varicella syndrome, characterized by hypoplasia of an extremity, skin abnormalities, encephalitis, microcephaly, ocular abnormalities, mental retardation, and low birth weight, may occur among 0.4 - 2.0% of infants born to women infected with varicella during the first half of pregnancy.

Although immunity following varicella infection is considered to be long lasting, second cases of varicella do occur rarely among immunologically normal persons and may be more common than previously thought. VZV is capable of remaining in a latent state in human nerve tissue and may reactivate in approximately 15% of infected persons resulting in herpes zoster (shingles). Herpes zoster usually presents as a vesicular rash with pain and itching in a dermatomal distribution. This disease is more common with increasing age, among immunocompromised persons and among children with a history of intrauterine varicella or varicella occurring within the first year of life; the latter have an increased risk of developing herpes zoster at an early age. Loss, or a relative absence, of cell-mediated immunity is considered to be the common factor in development of herpes zoster in these groups.

II. Background

Before the availability of varicella vaccine in the United States, almost everyone developed varicella. Thus, the number of cases approximated the birth cohort over time resulting in the 1990s in an estimated 4 million cases of varicella annually with approximately 11,000 hospitalizations and 100 deaths each year. Varicella affects mainly children, with approximately 90% of cases occurring before the age of 15 years. In the 1970s and 1980s, the highest rates of disease were among children 5-9 years of age followed closely by children 1-4 years of age.[1] In the 1990s, the highest rate of disease has been reported in the pre-school age group. This may have been due to increasing attendance at day care and/or pre-school.[6,7]

Varicella vaccine was licensed in 1995 and is recommended for routine use in infants 12 –18 months of age and for susceptible older children, adolescents and adults.[8-10] National vaccine coverage among children 19-35 months was 34% from July 1997 to June 1998 (with state and urban estimates ranging from 6% to 52%) and was 48% in the third quarter of 1998 (CDC, unpublished data). Data from active surveillance sites for varicella demonstrate that varicella disease incidence declined with vaccine coverage among children 1-2 years of age of 40-70% and with some evidence of catch-up vaccination among older children. Among states that have been consistently reporting a high proportion of cases to NETSS relative to their birth cohort (West Virginia and Michigan), there has also been a reduction in cases noted during the 1999 varicella season.

III. Importance of rapid case identification

Although rapid case identification of all suspected cases of varicella is not feasible, varicella can be prevented among susceptible exposed persons by prompt vaccination with varicella vaccine. Reporting of varicella in settings in which outbreaks are likely (e.g., day care centers or schools) will facilitate public health action in such circumstances. In addition, in certain high-risk settings (e.g., hospitals and other health-care settings), rapid case identification and public health action are important to prevent infection of susceptible persons at high risk for serious complications of varicella, such as immunocompromised persons and pregnant women.[8]

Post-exposure use of varicella vaccine and VZIG

The ACIP recommends the use of varicella vaccine for susceptible persons following exposure to varicella.[9] Varicella vaccine, if administered within 72 hours and possibly up to 120 hours following varicella exposure may prevent or significantly modify disease.[11,12,13] If exposure to varicella does not cause infection, post-exposure vaccination with varicella vaccine should induce protection against subsequent infection. If the exposure results in infection, the vaccine may reduce the severity of the disease. There is no evidence that administration of varicella vaccine during the incubation period of illness increases the risk for vaccine-associated adverse events.

Varicella zoster immune globulin can be ordered from the distributor (FFF Enterprises, Inc., Temecula, CA) by calling 800-843-7477.

Varicella zoster immune globulin (VZIG) is recommended for postexposure prophylaxis of susceptible persons who are at high risk for developing severe disease.[8] VZIG is most effective in preventing varicella infection when given within 96 hours of varicella exposure. The decision to administer VZIG to a person exposed to varicella should be based on 1) whether the person is susceptible, 2) whether the exposure is likely to result in infection, and 3) whether the patient is at greater risk for complications than the general population. Such groups would include newborn infants whose mothers developed varicella around the time of delivery (< 5 days before to 2 days after delivery), immunocompromised children, susceptible pregnant women, hospitalized premature infants >28 weeks gestation whose mother had no history of varicella, and premature infants <28 weeks gestation regardless of the mother's history of varicella.[8] Varicella zoster immune globulin can be ordered from the distributor (FFF Enterprises, Inc., Temecula, CA) by calling 800-843-7477.

IV. Importance of surveillance

Varicella can be prevented among susceptible exposed persons by prompt vaccination with varicella vaccine. Surveillance of varicella in institutions in which spread of disease is likely (e.g., day care centers and schools) is important in order to facilitate public health action and prevent outbreaks.

In addition, surveillance data are needed to 1) document and monitor the impact of a vaccination program on disease incidence, morbidity and mortality; 2) evaluate the effectiveness of prevention strategies; and 3) evaluate vaccine effectiveness under conditions of routine use. Increasing use of vaccine among children has lowered the overall burden of disease. However, among the greatly reduced number of remaining cases, a higher proportion will occur among older children, adolescents and adults.

Surveillance data can be used to evaluate vaccine effectiveness under conditions of routine use. Pre-licensure studies, using different vaccine formulations, showed vaccine efficacy ranging from 70% to 90% for all disease and >95% for severe disease. Post-licensure studies under conditions of community use demonstrated vaccine effectiveness of 85-91% for all disease and 100% for severe disease (CDC, unpublished data).[14] However, in some settings field effectiveness may be affected by improper storage and handling of vaccine at any stage of the cold chain. While mild "breakthrough" varicella may be expected to occur in 10% to 20% of vaccinated children, the rate of varicella (mild or severe) among vaccinated children should be monitored; if the rate of breakthrough disease is higher than expected (for example $\geq$ 30%), the cause of the problem should be investigated.

V. Disease reduction and vaccine coverage goals

Proposed Healthy People 2010 goals for varicella include: >90% reduction in varicella cases, >90% vaccine coverage among children 19-35 months, and > 95% vaccine coverage among children at school entry.[15]

VI. Case definition

The following case definitions were approved by the Council of State and Territorial Epidemiologists (CSTE) for varicella in June 1999[16] and for varicella deaths in 1998.[17]

Varicella

Clinical description

An illness with acute onset of diffuse (generalized) maculopapulovesicular rash without other apparent cause. In vaccinated persons who develop varicella more than 42 days after vaccination (breakthrough disease), the disease is almost always mild with fewer than 50 skin lesions and shorter duration of illness. The rash may also be atypical in appearance (maculopapular with few or no vesicles).

Laboratory Criteria for Diagnosis

- Isolation of varicella-zoster virus (VZV), or demonstration of VZV antigen by direct fluorescent antibody (DFA) or polymerase chain reaction (PCR) tests from a clinical specimen, or

- Significant rise in serum varicella immunoglobulin G antibody level by any standard serological assay

Case Classification

Probable: a case that meets the clinical case definition, is not laboratory confirmed, and is not epidemiologically linked to another probable or confirmed case

Confirmed: a case that is laboratory confirmed or that meets the clinical case definition and is epidemiologically linked to a confirmed or a probable case

Comments: Two probable cases that are epidemiologically linked would be considered confirmed, even in the absence of laboratory confirmation.

Varicella Death

Laboratory Criteria for Diagnosis

- Isolation of varicella-zoster virus (VZV), or demonstration of VZV antigen by direct fluorescent antibody (DFA) or polymerase chain reaction (PCR) tests from a clinical specimen, or

- Significant rise in serum varicella immunoglobulin G antibody level by any standard serological assay

Case Classification

Probable: a probable case of varicella which contributes directly or indirectly to acute medical complications which result in death.

Confirmed: a confirmed case of varicella which contributes directly or indirectly to acute medical complications which result in death.

Other definitions

Vaccine rash. A varicella-like rash in a child recently vaccinated for varicella is defined as a vaccine rash. Approximately 4% of children receiving varicella vaccine develop a generalized rash (as compared with 2% of placebo recipients), with a median of five lesions 5 to 26 days post-vaccination, and 4% develop a localized rash, with a median of two lesions, 8 to 19 days post-vaccination. The rash may be atypical in appearance (maculopapular with no vesicles). Rash occurring within 7 days of vaccination should be considered wild-type virus.

Breakthrough disease. Breakthrough disease is defined as a case of wild-type varicella infection occurring more than 42 days after vaccination. Such disease is almost always mild with shorter duration of illness, absence of fever and fewer than 50 skin lesions.

Secondary transmission of vaccine virus. Secondary transmission of vaccine virus is defined as a varicella-like rash occurring 10-63 days after exposure to vaccine virus.

VII. Laboratory testing

Laboratory testing for varicella is not routinely required, but may be useful in special circumstances to confirm the diagnosis or to determine varicella susceptibility. Diagnostic tests used to confirm recent varicella infection include virus isolation and identification, in addition to serologic tests. For additional information on laboratory support for vaccine-preventable disease surveillance, see Chapter 19.

Virus isolation and identification

- **Rapid varicella zoster virus identification**. Rapid virus identification techniques are indicated for a case with severe or unusual disease to initiate specific antiviral therapy. The direct fluorescent antibody (DFA) test is the method of choice for rapid clinical diagnosis. This test is sensitive, specific and widely available. Results are available within several hours. Specimens are best collected from rubbing the base of a skin lesion, preferably a fresh fluid-filled vesicle. Other specimen sources such as nasopharyngeal secretions, blood, urine, bronchial washings, and cerebrospinal fluid are considered less acceptable

sources than skin lesions since positive test results from such specimens are much less likely. Because viral proteins persist after cessation of viral replication, DFA may be positive when viral cultures are negative.

- **Virus culture.** The diagnosis of VZV infection may be confirmed by culture (isolation) of VZV. Although the virus is difficult to culture, virus isolation should be attempted in cases of severe disease, especially in immunocompromised persons, in order to confirm the diagnosis of varicella. Newer, more sensitive and rapid culture techniques may provide results within 2 to 3 days. Infectious VZV is usually recoverable from fluid from varicella lesions for 2 to 3 days and from zoster lesions for 7 days or longer. VZV may be cultured from other sites such as blood and CSF, especially in immunocompromised patients.

- **Virus strain identification**. Strain identification can distinguish wild VZV from the vaccine (Oka/Merck) strain. Because virus typing or strain identification using polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP) analysis is labor-intensive and time consuming, it should only be undertaken in special circumstances where it is important to distinguish wild from vaccine virus. Such situations post-vaccination include 1) rash with greater than 50 lesions; 2) suspected secondary transmission of the vaccine virus; 3) herpes zoster; or 4) any serious adverse event. The National VZV Laboratory at CDC has the capacity to distinguish wild-type VZV from Oka strain. Call (404) 639-0066 for details about the collection and submission of specimens for testing.

Serologic testing

Serological tests are available for IgG and IgM antibodies to VZV. Testing using commercial kits for IgM antibody is not recommended since available methods lack sensitivity and specificity; false positive IgM results are common in the presence of high IgG levels. The National VZV Laboratory at CDC has developed a reliable IgM capture assay. Call (404) 639-0066 for details about the collection and submission of specimens for testing.

Single serological IgG tests may be used to identify the immune status of individuals whose history of varicella is negative or uncertain, and who may be candidates for VZIG or vaccination. Paired acute and convalescent antibody tests are used in situations of mild or atypical presentation of disease when immediate therapy is not indicated and when, for clinical reasons, a confirmed diagnosis of the acute illness is important, e.g., a suspected second infection due to varicella.

VIII. Reporting

Each state and territory has regulations and/or laws governing the reporting of diseases and conditions of public health importance.[18] These regulations/laws list the diseases that are to be reported and describe those persons or institutions responsible for reporting, including health-care providers, hospitals,

laboratories, schools, day care facilities, and other institutions. Contact the state health department for reporting requirements in your state.

Reporting to CDC

Varicella deaths. In 1998, the Council of State and Territorial Epidemiologists recommended that varicella-related deaths be placed under national surveillance[17] and varicella-related deaths became nationally notifiable on January 1, 1999.

Varicella deaths can be identified through death certificates, which may be available through the state vital records systems and may be more readily available soon after death in states using electronic death certificates. State public health departments may also request that local health departments, practitioners and hospitals report varicella deaths that occur in their community.

All deaths due to varicella should be investigated to understand why a death resulted from this vaccine-preventable disease. The investigation may provide insight into risk factors for varicella mortality, and may help identify "missed opportunities" for, and barriers to, vaccination. A worksheet has been provided to guide varicella death investigations (Appendix 22).

Information to collect

The following data are epidemiologically important and should be collected in the course of a death investigation. Additional information may be collected at the direction of the state health department.

- Demographic information including state of residence, age, sex, country of origin, and years of residence in the US

- Medical history
  - -Pre-existing medical conditions
  - -History of varicella (to potentially distinguish varicella from herpes zoster)
  - -Medications

- Vaccination status including
  - -Number of doses of varicella vaccine
  - -Date(s) of vaccination
  - -If not vaccinated, describe reason

- Clinical and epidemiological data
  - -Date of rash onset
  - -Hospitalization, date of hospital admission
  - -Date of death
  - -Postmortem exam results
  - -Death certificate diagnosis

- Complications

-Pneumonia
-Infections - [e.g., invasive group A beta-hemolytic streptococcus (GAS), cellulitis, sepsis, necrotizing fasciitis]
-Encephalitis
-Hemorrhagic complications
-Reye syndrome

- Treatment including
  -Medications given (e.g., antiviral drugs, VZIG, aspirin, non-steroidal anti-inflammatory drugs)
  -Duration of therapy

- Laboratory information including
  -Virus isolation
  -DFA
  -Serology
  -PCR

- Epidemiological information including
  -Transmission setting
  -Source of transmission (e.g., age, vaccination status, relationship to decedent)

Varicella case reporting

Although individual case investigations are not yet routinely recommended, CSTE has recommended that all states carry out some form of ongoing systematic morbidity surveillance to monitor the impact of varicella vaccination on the incidence of varicella.[19] States are encouraged to report aggregate case counts to the National Notifiable Disease Surveillance System (NNDSS) by age group via the National Electronic Telecommunications System for Surveillance (NETSS). Contact your state health department for specific requirements in your state.

Although reporting and investigation of all cases of varicella is not feasible in most areas, action may be required to prevent transmission to susceptible persons at high risk of serious complications of varicella, such as might occur in a hospital setting.[8,20] A worksheet has been designed to provide guidelines for varicella case investigations in these special circumstances (Appendix 23).

IX. Vaccination

The Oka/Merck live attenuated varicella vaccine was licensed in the United States in March 1995. Because of the thermolability of the vaccine, the manufacturer's requirements for maintaining the cold chain must be followed strictly. Vaccine that is not properly stored before administration could have suboptimal potency.[8]

Routine administration of live attenuated varicella virus vaccine is recommended for children 12-18 months of age. Catch-up vaccination is

recommended for children 19 months through 12 years. One dose of vaccine is required for children aged < 13 years. A positive history of varicella is considered reliable evidence of immunity. For persons ≥ 13 years of age, the Advisory Committee on Immunization Practices (ACIP) recommends varicella vaccination for susceptible adolescents and adults who may have close contact with susceptible persons at high risk for serious complications (such as health-care workers and family contacts of immunocompromised persons) and for those at increased risk of exposure or transmission (teachers of young children, day-care employees, residents and staff in institutional settings or correctional facilities; nonpregnant women of childbearing age; adolescents and adults living in households with children; and international travelers).[8,9] However, vaccination is desirable for all susceptible adolescents and adults.[8] Adolescents ≥13 years of age and adults require 2 doses of varicella vaccine given 4 to 8 weeks apart. Serologic testing of adolescents and adults with an uncertain or negative history is likely to be cost-effective since 70%-90% of such individuals are likely to be varicella-immune.[8]

Note: Women should avoid pregnancy for 1 month after receiving a dose of varicella vaccine. Varicella vaccination is contraindicated in pregnancy. If inadvertent vaccination of a pregnant woman occurs, the incident should be reported to the Varivax® in Pregnancy Registry at 1-800-986-8999.

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X. Enhancing surveillance

Although individual cases of varicella are not nationally notifiable, surveillance is needed to facilitate public health action at the state and local level and monitor the impact of the varicella immunization program. Several approaches may be used to monitor trends in varicella disease burden and vaccine effectiveness.[21]

Report aggregate cases by age group. States are encouraged to report aggregate case counts for varicella to the National Notifiable Diseases Surveillance System (NNDSS). Reporting varicella by age group improves the ability to detect changes in age-specific incidence for varicella.

Conduct sentinel and school-based surveillance. Schools, child care centers, physicians' practices, and hospitals should be encouraged to report aggregate case counts of varicella by age group or grade. School reporting is influenced by the support of the principal, teachers and secretarial staff, as well as parental awareness of the importance of reporting varicella to the school. Some states conduct sentinel or school-based surveillance even though state-wide case reporting is not required. Sentinel sites can be limited to a geographic area such as a county or city, or selected to be representative of the state.

Search hospital discharge databases. Varicella morbidity should be monitored with ongoing review of hospital discharge databases for varicella diagnostic codes (ICD-9 052). These data also provide information on risk factors for severe disease. Medical record review can be used to validate accuracy of the hospital discharge database.

Perform telephone surveys. Telephone surveys have been used effectively to estimate age-specific incidence for varicella since it is an easily recognized disease and does not require physician confirmation of the diagnosis.[6,7] Surveys can be repeated to monitor changes in age-specific incidence. However, such surveys may be expensive and larger sample sizes will be required as disease incidence declines. Another limitation of this method is that it does not detect outbreaks and so does not lead to public health action.

Assess vaccine effectiveness. Vaccine effectiveness can be evaluated by comparing rates of disease among vaccinated and unvaccinated persons in outbreak settings such as may occur in schools or child care centers.[22] It is particularly important to evaluate whether varicella among vaccinated children is occurring at a rate higher than expected. Low vaccine effectiveness could indicate improper storage and handling of the vaccine, which has stringent cold-chain requirements.

XI. Case investigation

Although investigation of all cases of varicella is not feasible in most areas, action may be required to prevent transmission to susceptible persons at high risk of serious complications of varicella. In addition, investigation is warranted

in some specific circumstances, including: deaths associated with varicella; outbreak investigation; exposure of potentially susceptible persons at high risk of serious complications of varicella and documentation of severe complications such as invasive group A streptococcal infections. Because of the stringent cold-chain requirements of this vaccine, an investigation should be considered when a high proportion of cases occur among vaccinated persons. For more information or for assistance with case, outbreak, and death investigations, contact your state health department.

For varicella post-exposure prophylaxis of contacts, see section III.

XII. Outbreak investigation and control

Child care centers and schools are the most common sites for varicella outbreaks; children aged 1-9 years attending these facilities have the highest varicella susceptibility and disease incidence. Despite low susceptibility among adults (generally <5%), outbreaks have been reported from a variety of adult settings including correctional facilities, hospitals, military training facilities, refugee centers, immigration detention facilities, homeless shelters, other residential institutions, and cruise ships.

Investigation of outbreaks of vaccine-preventable diseases help us to understand whether outbreaks are occurring due to the failure of vaccine (lower than expected vaccine effectiveness) or failure to vaccinate (low vaccine coverage rates and therefore high susceptibility.) Investigation of varicella outbreaks can provide estimates of varicella vaccine effectiveness in different outbreak settings and may identify risk factors for vaccine failure. In the course of investigation, health authorities may use information on susceptibility and reliability of history in order to develop an appropriate screening and vaccination policy for the affected population (e.g., correctional facilities, residential institutions, the military). Because varicella outbreaks continue to be common, especially among children, state and local health departments may wish to focus investigation and control efforts on outbreak situations which may present the greatest risk of severe morbidity from varicella (Table 1).

A systematic approach to investigation and/or control of outbreaks includes confirming the outbreak, identifying susceptible persons, offering vaccine, establishing surveillance, analyzing data and using data to make recommendations. These steps are outlined in Table 2, and are presented in more detail in Appendix 24.

Outbreak control

Varicella vaccine is recommended by the ACIP for outbreak control.[9] Options for outbreak control are:

1. Isolate infected cases and distribute a letter recommending vaccination

The response to an outbreak may involve one or a combination of measures that include isolation of infected persons and vaccination with varicella vaccine.

Isolation (exclusion) or cohorting of individuals with varicella until all of their lesions have crusted is routinely recommended for outbreak control. However, because substantial transmission of chickenpox occurs before rash onset, exclusion may have limited value as an outbreak control measure.[23] Exclusion is also recommended for exposed susceptible individuals who may be in contact with persons at high risk of serious complications (e.g., health care workers and family members of immunocompromised persons). In these situations, exclusion is required for the duration of the period of communicability (i.e., from the 10th until the 21st day post-exposure).[8,20]

For outbreaks in day care centers and schools, ***informing parents/care givers of the occurrence of the outbreak, information on varicella and its potential to cause severe complications as well as the availability of the vaccine is the minimum public health response to an outbreak.*** Varicella vaccine, if administered soon after exposure, can prevent or significantly modify varicella in exposed, susceptible persons. Thus, transmission of varicella can be prevented by vaccination.

A sample letter to parents is provided in Appendix 24. This letter recommends that parents/care givers contact their regular health care provider to discuss the use of the vaccine for their child. To encourage use of the vaccine, health departments may choose to send letters to all child care facilities and elementary schools in the state. A Vaccine Information Statement should be included with the letter.

2. Vaccinate susceptible persons with varicella vaccine

In institutional outbreaks, vaccination of susceptible persons should be strongly considered. Varicella vaccine is effective in prevention of varicella in susceptible, exposed persons if administered soon after exposure (see above). Health department personnel and officials in other institutions (e.g., health care settings, correctional facilities) should evaluate available resources and consider vaccination of susceptible persons for outbreak control. ❖

Table 1. Varicella outbreaks: priorities for investigation
1. Outbreaks among patients and staff in health-care settings (top priority for investigation)
2. Outbreaks associated with severe complications (e.g., pneumonia, encephalitis, serious infectious complications such as invasive Group A streptococcal infection or hemorrhagic complications) and/or hospitalizations
3. Outbreaks among persons who are immunocompromised due to HIV infection, cancer, or immunosuppressive therapy
4. Outbreaks involving adolescents and adults
5. Outbreaks involving infants aged <12 months in child care centers
6. Clusters of reports (may suggest improper storage and handling of vaccine)
7. Outbreaks involving a large number of cases
8. Outbreaks occurring among vaccinated populations.

Table 2. Steps for investigation and control of varicella outbreaks

1. Confirm outbreak, investigate cases and determine varicella susceptibility
    - a. Define cases and confirm outbreak
    - b. Screen for susceptibility to varicella
        - i. Verify history of disease and vaccination and/or
        - ii. Use serologic testing
    - c. Investigate cases to characterize illness including onset, severity, duration, pre-existing medical conditions and medications, and complications
2. Initiate outbreak control and treat cases (if appropriate):
    - a. Isolate or cohort infective cases
    - b. Recommend treatment of active cases with antiviral therapy (adolescents and adults)
    - c. Offer vaccine to susceptible persons
        - i. Distribute letter recommending vaccination, or
        - ii. Offer vaccine through on site clinic
    - d. Offer VZIG to exposed, susceptible persons at high risk of severe disease
3. Establish surveillance for:
    - a. Additional varicella cases
    - b. Vaccine-associated adverse events
4. Analyze collected data:
    - a. Describe cases and transmission (e.g., date of rash onset, age, sex, country of origin)
    - b. Describe serological status (if serology testing performed)
    - c. Evaluate outbreak control efforts
    - d. Calculate vaccine effectiveness
5. Investigate low vaccine effectiveness (if present)

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